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ABSTRACT

BACKGROUND: Genome-wide association studies have identified numerous genetic variants that predispose to neuropsychiatric traits. Identification of mechanisms in the brain that underlie these associations is essential for understanding manifestations of genetic predisposition within the general population. Here, we investigated the association between polygenic scores (PGSs) for seven neuropsychiatric traits and white matter microstructure of the brain on diffusion tensor imaging in the pediatric population.

METHODS: Participants from the Generation R Study who had genotype and diffusion tensor imaging data available (n = 1138, mean age = 10.2 years, range = 8.7–12.0) were included. PGSs were calculated for five psychiatric disorders (attention-deficit/hyperactivity disorder, bipolar disorder, autism, major depressive disorder, and schizophrenia) and two cognitive traits (intelligence and educational attainment) and were tested for associations with global and tract-specific fractional anisotropy (FA) and mean diffusivity.

RESULTS: Significant positive associations with global FA were observed for the PGSs of intelligence (β = .109, SE = .029, $p < .001$, ΔR^2 = .012) and educational attainment (β = .118, SE = .029, $p < .001$, ΔR^2 = .014). No significant associations were observed with FA for the PGSs of psychiatric disorders. Tract-specific analysis showed that the PGSs for intelligence and educational attainment were associated with FA of several association and projection fibers of the brain.

CONCLUSIONS: Our results show that genetic predisposition for cognition-related traits, but not for psychiatric disorders, is associated with microstructural diffusion measures of white matter tracts at an early age. These results suggest a shared genetic etiology among structural connectivity, intelligence, and educational achievement.

Keywords: Children, Cognition, DTI, Polygenic scores, Psychiatric disorders, White matter

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Recent genome-wide association studies (GWASs) have improved insight into the highly complex polygenic architecture of human behavioral traits, including psychiatric disorders (1–3) and cognitive ability (4,5). The rapid discovery of genetic variants has created the need for identification of downstream mechanisms in order to understand the biological impact of genetic risk on a system level (6–8). Recent studies have used polygenic scoring analyses to estimate overall genetic risk for psychiatric disorders and test the combined effects of thousands on single nucleotide polymorphisms (SNPs) on brain imaging–derived phenotypes using magnetic resonance imaging (MRI) (9). Indeed, structural brain imaging studies in the general population have shown associations with disease-related alterations in healthy individuals carrying a high polygenic score (PGS) for psychiatric illness, including differences in gyrification patterns (10) and cortical thickness (11). Functional imaging studies have shown that polygenic risk for schizophrenia can be linked to different brain activity during tasks (12,13) and during rest (14), illustrating the complex combined downstream effects on brain functioning. In addition, evidence of brain differences in healthy subjects at high genetic risk has also been suggested by imaging studies in high-risk individuals having a first-degree relative with a psychiatric disorder, which showed abnormalities in a variety of structural (15–17) and functional (17–19) measures of the brain. However, so far only a few studies have investigated associations of polygenic risk with white matter fibers of the brain (20,21), even though the structural connectivity of the brain is known to be related to major psychiatric disorders, including schizophrenia (22) and bipolar disorder (23,24), as well as to normal cognitive functioning (25,26), and white matter changes have been observed in healthy relatives of patients with psychiatric disorders (27,28). In addition, most prior genetic studies included only GWAS-significant SNPs ($p < 5 \times 10^{-8}$) in the PGS and do not take the contribution in genetic signal of subthreshold SNPs into account (29). Moreover, prior studies have almost exclusively focused on adolescents or adults, while deviation from normal brain

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development may be present much earlier in life. Here, we investigated whether genome-wide PGSs for psychiatric traits and cognitive ability are associated with white matter microstructure on diffusion tensor imaging (DTI) of the brain in a large population-based cohort of children between 9 and 12 years of age. Insight into a possible shared genetic etiology among psychiatric disorders, cognitive ability, and white matter microstructure provides further understanding of neurobiological manifestations of genetic predisposition for psychopathology and cognition at an early age in the general population.

METHODS AND MATERIALS

Study Sample

The current study was conducted within the Generation R Study, a population-based cohort studying multifaceted aspects of child development (30). Between March 2013 and November 2015, participants were enrolled in the cohort's MRI study with the aim of studying brain development in the general population by collecting high-quality, single-scanner MRI data of the brain (31). The current study included unrelated participants of European ancestry who had good-quality MRI data available and from whom genotype data had been collected previously. The Medical Ethics Committee of the Erasmus University Medical Center approved the study protocol, and the legal representatives of the participants provided written informed consent.

Diffusion Tensor Imaging

DTI of the brain was performed on a single study-dedicated 3T MR750w Discovery MRI scanner (General Electric, Milwaukee, WI). Twelve major white matter tracts were identified using probabilistic tractography. Diffusion characteristics within these tracts were used to quantify mean fractional anisotropy (FA) and mean diffusivity (MD). A detailed description of the imaging procedures, scan protocol, and subsequent processing of the DTI data is provided in the Supplement.

Confirmatory factor analysis was applied using the lavaan R package (32) to model a single latent factor of global FA and MD, as described by Muetzel *et al.* (25). White matter tracts included in the model and standardized factor loadings on the global factor are shown in Figure 1 and Supplemental Tables S1 and S2. The global factors were tested for association with the PGS in univariate analyses.

Genotype Data

Genotype data were collected at birth or during a visit to the research center using Illumina 610K and 660K genotype arrays (Illumina, San Diego, CA). Data collection and subsequent processing procedures have been described previously (33). Additional quality control procedures of the genotype data and genotype imputation are described in the Supplement.

Polygenic Scoring

PGSs were calculated on imputed genotype data using publicly available GWAS results for five psychiatric disorders and two cognitive traits: attention-deficit/hyperactivity disorder (ADHD), autism spectrum disorder, bipolar disorder, major depressive disorder, schizophrenia, intelligence, and educational attainment. An overview of the discovery GWASs is provided in Supplemental Table S3. Because the Generation R cohort was included in the GWAS of intelligence, the GWAS was repeated after exclusion of the Generation R cohort

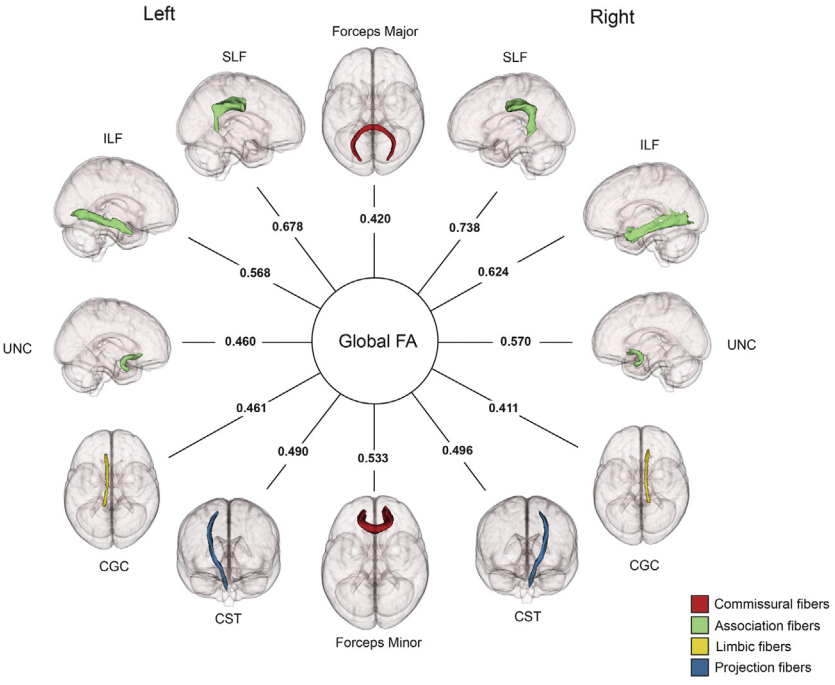

Figure 1. Standardized factor loadings of white matter tracts included in the global factor of fractional anisotropy (FA). Global factors for FA were estimated using confirmatory factor analysis. White matter tracts are color coded according to subcategory. CGC, cingulum bundle; CST, corticospinal tract; ILF, interior longitudinal fasciculus; SLF, superior longitudinal fasciculus; UNC, uncinate fasciculus.

(sample size after exclusion = 267,938). Generation R was not included in any of the other six GWASs. PGSs were calculated using PRSice (34), a script for calculation of PGS in PLINK (35). We calculated PGSs based on several *p*-value thresholds (p_T) for inclusions of SNPs in the score ($p_T < .001$, .005, .01, .05, .1, .5, and 1). We tested multiple thresholds to find the optimal threshold that has the strongest association with the outcome. PGSs were subsequently standardized to a mean of 0 and an SD of 1 for interpretability. The number of SNPs that were included in each PGS and threshold is shown in Supplemental Table S4.

Statistical Analysis

Statistical analyses were performed using the R statistical software (36) (version 3.2.1). Association testing was performed in a hierarchical approach. First, a global factor of white matter microstructure was predicted from the confirmatory factor analysis model and regressed on the PGS. Next, in secondary analyses, we studied tract-specific associations by regressing the individual white matter tracts on the PGS *p*-value threshold that showed the strongest association with the global factor in the primary analysis (lowest *p* value). All analyses were corrected for age, sex, and four genetic principal components as covariates. False discovery rate was used to correct for multiple testing (37). Correction was applied to the total number of statistical tests for each risk score, *p*-value threshold, and global and tract-specific diffusion measures. A false discovery rate–corrected significance threshold was applied, and *p* values below .004 were considered statistically significant.

RESULTS

Sample Characteristics

A total of 3992 participants underwent MRI of the brain. DTI was completed in 3786 of these participants. After DTI quality control procedures, 3279 participants remained. Of these participants, 1920 individuals had genotype data available. Subsequent filtering based on European ancestry, relatedness, and genotype quality resulted in 1138 participants who were included in the study (see flowchart in Supplemental Figure S1). The mean age of the sample was 10.2 years (range = 8.72–11.99), with a balanced distribution of sex (50.6% boys). The mean standardized PGSs for educational attainment and intelligence were slightly higher compared with the genotyped participants of European ancestry who did not participate in the MRI study (educational attainment: 0.058 vs. −0.039, $t = 2.56$, $p = .01$; intelligence: 0.099 vs. −0.067, $t = 4.39$, $p = 1.17 \times 10^{-5}$) (Supplemental Table S5) and were lower for ADHD (−0.055 vs. 0.036, $t = -2.39$, $p = .02$) and depression (−0.071 vs. 0.047, $t = -3.09$, $p = .002$). There was a moderate correlation among several PGSs (see correlation heatmap in Supplemental Figure S2), showing the largest correlation between the educational attainment and intelligence PGSs ($r^2 = .38$–$.47$ between different *p*-value thresholds).

Associations With IQ

We tested whether the PGSs of intelligence and educational attainment were associated with nonverbal IQ, measured in a subsample of 982 participants around 6 years of age. The PGSs of intelligence and educational attainment were strongly associated with nonverbal IQ, explaining approximately 5% by the PGS of intelligence ($\beta = .222$, SE = .032, $p = 1.87 \times 10^{-12}$, $\Delta R^2 = .050$) (Supplemental Table S6).

Global FA/MD

Explained variance (ΔR^2) in the global factor of FA and MD by the PGS is shown in Figures 2 and 3, respectively, and full regression results are shown in Supplemental Tables S7 and S8. The PGS of intelligence showed positive associations with global FA across different *p*-value thresholds, with the strongest being the PGS based on a *p*-value threshold of $p_T < .005$ ($\beta = .109$, SE = .029, $p < .001$, $\Delta R^2 = .012$) (Figure 2). Similarly, we observed positive associations across all *p*-value thresholds for the PGS of educational attainment, explaining approximately 1.4% of the variance in global FA at the *p*-value threshold of $p_T < 1$ ($\beta = .118$, SE = .029, $p < .001$, $\Delta R^2 = .014$). We did not observe significant associations between the global factor of FA and the PGSs of the five psychiatric traits after correcting for multiple testing. In addition, none of the seven

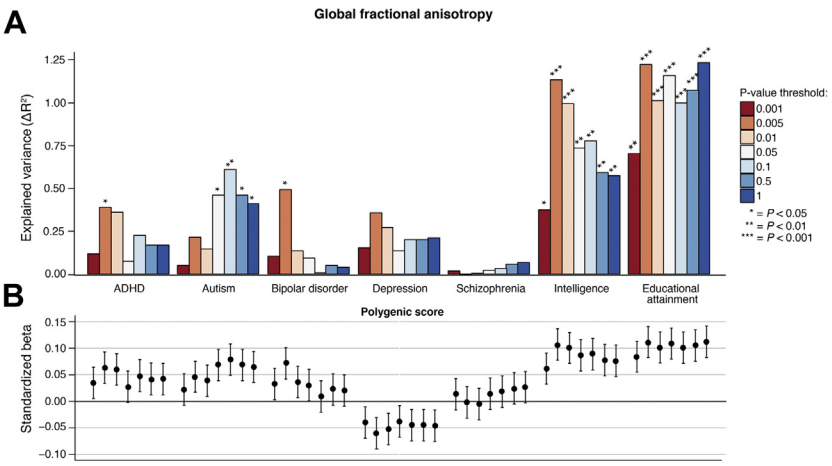

Figure 2. Variance explained in global fractional anisotropy by polygenic scores. **(A)** Variance explained (ΔR^2) in global fractional anisotropy by the polygenic score. **(B)** Standardized regression coefficients of associations between the different polygenic scores and global fractional anisotropy for each *p*-value threshold corrected for age, sex, and four genetic principal components. ADHD, attention-deficit/hyperactivity disorder.

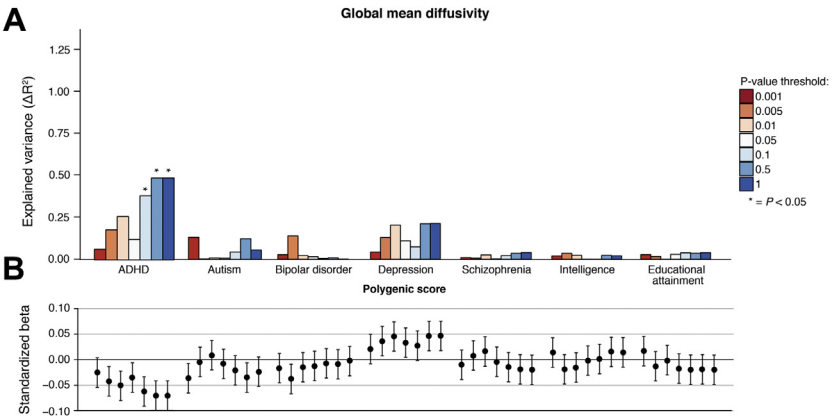

Figure 3. Variance explained in global mean diffusivity by polygenic scores. **(A)** Variance explained (ΔR^2) in the global factor of mean diffusivity by the polygenic score. **(B)** Standardized regression coefficients of the polygenic score on global mean diffusivity for each individual *p*-value threshold corrected for age, sex, and four genetic principal components. ADHD, attention-deficit/hyperactivity disorder.

PGSs showed associations with the global factor MD that survived multiple testing correction (Figure 3).

Tract-Specific Analysis

To test whether associations with specific white matter tracts could explain the association between the PGS and global FA, we performed univariate associations with diffusion measures FA and MD of individual white matter tracts. PGSs based on the *p*-value threshold that showed the strongest association with the global factor of FA and MD in the primary analysis (lowest *p* value) were tested for tract-specific associations. Figure 4 shows the association results between the PGS and FA and MD in each white matter tract, and a full overview of the regression results is provided in Supplemental Tables S9 and S10. Effect sizes for intelligence and educational attainment are represented visually in Figure 5.

The PGS of intelligence showed positive associations with tract-specific FA in four major white matter tracts: the right superior longitudinal fasciculus ($\beta = .125$, SE = .029, $p < .001$), the left inferior longitudinal fasciculus ($\beta = .087$, SE = .029, $p < .001$), and both the left and right corticospinal tracts (left: $\beta = .132$, SE = .029, $p < .001$; right: $\beta = .148$, SE = .029, $p < .001$). Associations between educational attainment PGS and white matter tract partially overlapped with results of intelligence PGS and showed similar positive associations with the right superior longitudinal fasciculus ($\beta = .118$, SE = .029, $p < 0.001$), and the left and right corticospinal tracts (left: $\beta = .107$, SE = .029, $p < .001$; right: $\beta = .092$, SE = .029, $p < .001$). In addition, significant associations were observed with the right inferior longitudinal fasciculus ($\beta = .105$, SE = .029, $p < .001$) and the forceps minor ($\beta = .088$, SE = .029, $p < .001$). Tract-specific FA was not associated with the psychiatric PGS. For tract-specific MD values, we observed a significant positive association between the intelligence PGS and the forceps major ($\beta = .105$, SE = .029, $p < .001$), whereas a negative association was observed between the ADHD PGS and MD of the forceps minor ($\beta = -.088$, SE = .029, $p < .001$).

DISCUSSION

In this study, we observed positive associations between genetic predisposition for cognition-related traits and white matter microstructure on MRI in the pediatric population, with the PGSs of intelligence and educational attainment explaining approximately 1% of the variance in global FA. Tract-specific analyses showed that these associations are driven by several association and project fibers of the brain. These results may suggest a shared genetic etiology among global white matter integrity, general cognitive functioning, and predicted later-life educational achievement.

Previous research showed that the PGS of educational attainment is associated with general intelligence but has also been associated with socioeconomic status (38) and later-life outcomes, including reproductive behavior (39) and longevity (40). To date, genetic variants related to cognitive traits have only been linked to total intracranial volume on MRI based on GWAS summary statistics using linkage disequilibrium score regression (41). Our study is the first to report significant associations between PGSs for intelligence and educational attainment and structural connectivity of the brain, emphasizing the important role of white matter microstructure in cognitive functioning. This finding is in line with previous work from our group that reported associations between nonverbal IQ and global FA (25) and specific associations with the superior longitudinal fasciculus. Our study adds to these findings that cognition and white matter microstructure are likely to share a common genetic architecture. We hypothesize that two underlying mechanisms may explain these observed associations. First, the discovery GWAS of educational attainment by Okbay *et al.* (5) reported that candidate genes near the 74 genome-wide significant variants showed elevated expression in the central nervous system. Moreover, these candidate genes were highly enriched for gene sets related to neurodevelopment such as sprouting of dendrites and synaptic plasticity. Similar gene set results were observed by Savage *et al.* (42) in the GWAS of intelligence, which highlighted that genes related to several cellular processes in neurons influence cognitive functioning. Given the associations between PGSs of intelligence and educational attainment and white matter microstructure in our study, it may be possible that similar molecular pathways and neurobiological processes lead to higher developed states of microstructural organization, which subsequently leads to a higher FA on DTI. Genetic studies of white matter integrity on DTI indeed

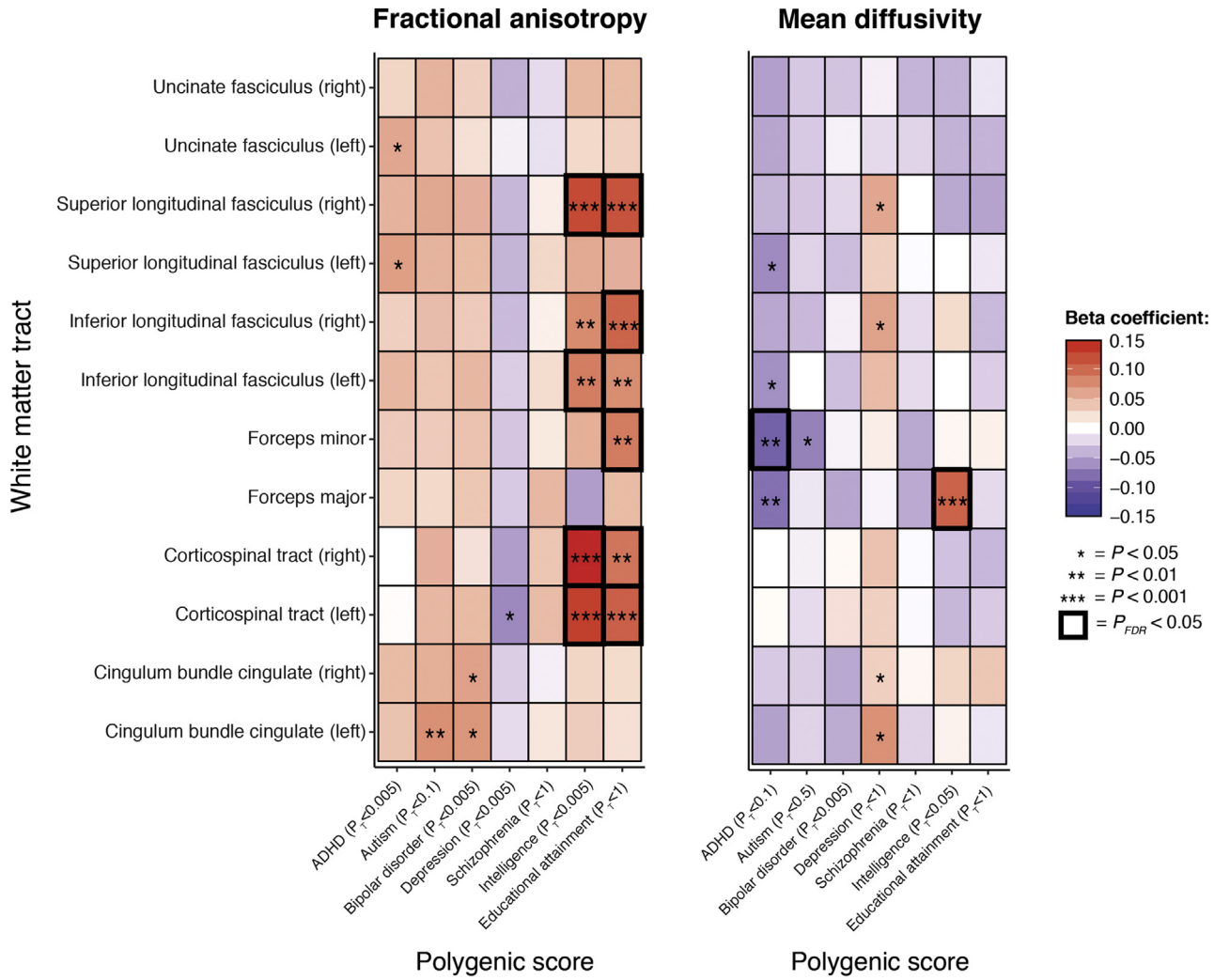

Figure 4. Tract-specific associations between polygenic scores and white matter tracts. Associations between polygenic scores and tract-specific fractional anisotropy and mean diffusivity are shown. Coefficients are standardized regression coefficients corrected for age, sex, and four genetic principal components. ADHD, attention-deficit/hyperactivity disorder; FDR, false discovery rate.

confirmed that genes involved in synaptic processes, such as neuronal transmission and cell adhesion, are important contributors to white matter microstructure (43). Second, given previously described associations between the educational attainment PGS of the child and parental socioeconomic status (44), gene–environment correlations with environmental factors that positively affect white matter microstructure, including prenatal factors (45), parenting strategies (46), and a healthy lifestyle (47), may amplify the observed associations. Considering that educational achievement is correlated with a broad range of environmental factors, it is possible that the educational attainment PGS captures the combined effect of a diverse array of factors that affect white matter development.

Interestingly, we did not observe associations between the schizophrenia PGS and white matter microstructure, which is surprising given extensive literature on white matter abnormalities in patients with schizophrenia (22), individuals at high genetic risk for schizophrenia as defined by family history (48,49), and associations between the schizophrenia PGS and behavioral problems in our sample as previously reported (50). We argue that several factors may explain this negative finding. First, at the age of our study sample (mean age of 10.2 years), white matter abnormalities described in patients with schizophrenia might be not yet present, not present on a scale detectable by DTI, or present but obscured by increased variance associated with different rates of white matter maturation between individuals. Moreover, MRI modalities examining structural phenotypes and activation patterns of the brain may be more sensitive to developmental changes related to the genetic risk for schizophrenia. Previous studies in healthy individuals indeed have shown associations between schizophrenia PGS and cortical morphology on structural imaging (10,11) and activation patterns during cognitive tasks on functional MRI (13,51). Second, the PGS in this study captures genetic signal only from common variants (minor allele frequency $>$ 0.01) of typically low individual effect sizes (52).

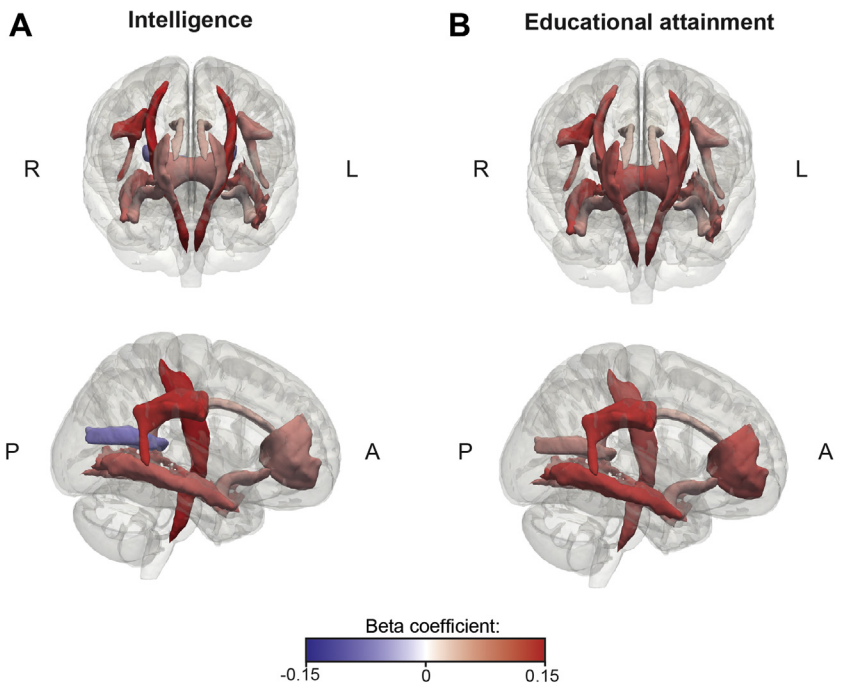

Figure 5. Visual representation of tract-specific associations between polygenic scores and white matter tracts. **(A)** Associations between the polygenic scores for intelligence and tract-weighted average fractional anisotropy. **(B)** Polygenic scores of educational attainment and tract-weighted average fractional anisotropy. Coefficients are standardized regression coefficients corrected for age, sex, and four genetic principal components. Regression results are shown in Supplemental Tables S8 and S9. A, anterior; L, left; P, posterior; R, right.

White matter alterations found in patients with schizophrenia may follow from more deleterious rare variants with comparatively larger effects and higher penetrance. Compelling evidence exists that these rare mutations contribute substantially to schizophrenia risk (53,54) and commonly disrupt neurodevelopmental processes (55,56), which could potentially underlie the observed microstructural abnormalities. Third, nonparticipation among high-risk individuals compared with low-risk individuals in population-based research has been previously described (57). Subsequent underrepresentation of individuals with the highest risk of schizophrenia may further explain this null result. In addition, no associations were observed for the PGSs of four other psychiatric traits. The absence of association for these traits may be partially explained by the GWAS small sample sizes (autism, depression, and bipolar disorder), the later onset of these disorders (depression and bipolar disorder), and/or an absent relation between white matter and these psychiatric disorders.

The current study has several strengths. First, the sample is large for imaging standards, especially in pediatric populations. Second, the sample comprised a narrow age range and the study was performed in a population-based cohort, which can minimize, but certainly not remove, age-related differences in white matter development. Third, all subjects were scanned on a single, research-dedicated MRI scanner using the same software version, removing possible noise from interscanner differences or changes associated with scanner upgrades. Fourth, PGSs for multiple traits were simultaneously tested, allowing for comparisons across traits in a single study sample. Some limitations are also present. First, the associations between PGS and white matter microstructure were tested using a cross-sectional design. Prospectively collected brain-imaging data could provide evidence on whether PGSs are associated with variation in trajectories of white matter development in children over time. Second, the current largest discovery GWASs used for calculating the PGSs of ADHD, autism, and bipolar disorder are less powered compared with other traits that were tested. As discovery sample sizes increase rapidly, we expect that PGS studies based on well-powered GWAS results will lead to more robust associations with brain imaging phenotypes. Lastly, polygenic risk scores do not provide insights into which SNPs contribute most to the observed associations with structural connectivity. Future genome-wide studies of structural connectivity in large DTI samples may further aid in estimating genetic overlap among cognitive functioning, psychiatric disorders, and structural connectivity and in identifying SNPs that are shared between these traits.

In conclusion, we report evidence that genetic predisposition for cognitive traits is associated with higher white matter microstructural integrity in children, whereas no associations were found for five major psychiatric disorders. Future studies are necessary to explore associations with longitudinal developmental trajectories of white matter microstructure over time.

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All authors report no biomedical financial interests or potential conflicts of interest.

ARTICLE INFORMATION

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